REMARKS

I. Status of the claims

The claims have been amended to clarify the nature of the invention. In particular, the phrase "therapeutically effective amount" has been removed from claims 1, 2, and 9. In addition, the term "selective" has been added to claims 1, 2, 3, 4, and 9 to better describe the cyclooxygenase-2 inhibitor and to better describe the leukotriene B_4 receptor antagonist. Support for the addition of "selective" to modify cyclooxygenase-2 inhibitors can be found on pages 7-8 of the specification and support for addition of "selective" to modify leukotriene B_4 receptor antagonist can be found on page 8 of the specification.

II. 35 U.S.C.112, First Paragraph Rejections

A. *Claims 1-2 and 6-9 satisfy the written description requirement*

Reconsideration is requested of the rejection of claims 1-2 and 6-9 under 35 U.S.C. §112, first paragraph. These claims were rejected on the basis that they do not satisfy the written description requirement.

Claim 1, as amended, is directed toward a **combination** comprising two recited compositions: a cyclooxygenase-2 selective inhibitor and a selective leukotriene B_4 receptor antagonist. The Office has asserted the specification fails to provide a representative number of examples. MPEP §2163(II)(3)(a)(ii) specifically dictates:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e, structure or other physical and /or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

In this case, the common attribute possessed by one of the compounds recited in claim 1 is its ability to inhibit cyclooxygenase-2 in a selective manner, and the

common attribute possessed by the other compound is its ability to function as a selective leukotriene B_4 receptor antagonist. The specification provides a detailed definition regarding exactly what constitutes a "selective" cyclooxygense-2 inhibitor as:

> ...compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

In addition, the specification provides a detailed definition regarding exactly what constitutes a "selective" leukotriene B_4 receptor antagonist as:

> ...compounds which selectively antagonize a leukotriene B_4 receptor with an IC_{50} of less than about 10 μM. More preferably, the leukotriene B_4 receptor antagonists have an IC_{50} of less than about 1 μM.

Moreover, the specification provides over 100 examples of compounds that selectively inhibit cyclooxygenase-2[1] and over 40 examples of compounds that are selective leukotriene B_4 receptor antagonist.[2] In excess of 100 examples and 40 examples cannot fairly be deemed to fall short of the "representative" number required by the MPEP and the statute. In view of this disclosure, therefore, a skilled artisan would conclude that the applicants were in possession of the combination recited in claim 1.

Applicants also request reconsideration of the assertion that the written description is not satisfied because the specification does not provide any guidance as to what **structural features** "all" compounds must have in order to possess either cyclooxygenase-2 selective inhibitory activity or leukotriene B_4 receptor antagonist activity.

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[1]See pages 5-6 and 11-18 of the specification.

[2]See pages 8-9 of the specification.

In particular, as stated above, it is **not required** that an applicant disclose "all" features possessed by each possible member of a genus for purposes of satisfying the written description requirement.[3] Moreover, case law is replete with examples where claims directed toward a combination of two or more compounds were found to satisfy the written description requirement when one or more of the compounds were described only functionally. By way of example, *in re Fuetterer,* the inventor claimed a composition for use in the production of rubber tires where one component of the composition was described only functionally as an "inorganic salt that is capable of holding a mixture of said protein and/or carbohydrate in colloidal suspension."[4] The Examiner rejected the inventor's claims as not satisfying the written description requirement, stating that "it is well established that claims should set out what the materials are and not by what they do."[5] The CCPA reversed the rejection, holding that it is permissible to use only terms of effect or result to the extent that the terms accurately describe essential qualities of a product to one skilled in the art.[6] According to the court, the essential qualities of the inorganic salt were sufficiently described solely by its ability to maintain other components of the composition in "colloidal suspension."[7]

In *In re Herschler*[8], the inventor claimed a combination comprising dimethyl sulfoxide (DMSO) and "a physiologically active steroidal agent" for use in enhancing penetration across a membrane and claimed priority dating back to the filing of a great-grandparent application. The Examiner rejected the claims in view of prior art published

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[3]See MPEP §2163(II)(3)(a)(ii).

[4]In re Fuetterer, 319 F.2d 259, 138 USPQ 217 (1963).

[5]Id at 262.

[6]Id at 264.

[7]Id at 264-265.

[8]In re Herschler, 591 F.2d 695, 200 USPQ 711 (1979).

after the filing date of the great-grandparent application stating in part that the claims were not entitled to the great-grandparent's filing date because the great-grandparent application lacked written description to support "a physiologically active steroidal agent" in view of disclosure of only 1 example (corticosteroid) to support the genus.[9] The CCPA reversed the rejection, holding that "the **use of known** chemical compounds in a manner auxiliary to the invention must have a corresponding written description **only so specific as to lead one having ordinary skill in the art to that class of compounds.**"[10] According to the court, steroids as a class of compounds when employed in a composition with DMSO are chemically similar.[11]

Analogous to the combination of *In re Fuetterer,* the combination of claim 1 describes "essential qualities" of each component of the combination to a skilled artisan. Both the cyclooxygenase-2 inhibitor and the leukotriene B_4 receptor antagonist are identified in claim 1 by their ability to either selectively inhibit a particular enzyme or selectively function as a receptor antagonist, just as the inorganic salt in *In re Fuetterer* was described solely by its ability to maintain other components of the composition in "colloidal suspension." Based upon the recited function of each component of the claim 1 combination, a skilled artisan would discern that the applicants were in possession of the invention.

Similar to the combination of *In re Herschler*, claim 1 is directed to a composition employing the use of **two known classes** of chemical compounds: cyclooxygenase-2 selective inhibitors and selective leukotriene B_4 receptor antagonist. As a class, "selectivity" is defined functionally in the specification for both cyclooxygense-2 inhibitors and leukotriene B_4 receptor antagonists such that a skilled artisan can readily distinguish members that belong to each class from those that do not (i.e. a "selective" compound from a non-selective compound) based upon the function of the particular

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[9] Id at 696.

[10] Id at 702 (emphasis added).

[11] Id at 701.

compound irrespective of the chemistry it may possess. Moreover, in *In re Herschler,* claims were directed to "a physiologically active steroidal agent" as a class of chemical compounds where the specification detailed only 1 example. In the instant case, the specification provides over 100 examples of compounds that selectively inhibit cyclooxygenase-2[12] and over 40 examples of compounds that are selective leukotriene B_4 receptor antagonist.[13] If the CCPA determined that a functional description and one example satisfied the written description requirement, applicants' functional description plus 100 and 40 examples which have the respective common attribute required in the claim, namely, selectivity for cyclooxygenase-2 and leukotriene B_4 antagonist selectivity, respectively cannot fairly be deemed to be a insufficient description.

In view of this comprehensive disclosure and relevant case law, one skilled in the art would discern that applicants were in possession of the combination detailed in claim 1. Moreover, claims 2 and 6-9, which depend from claim 1, satisfy the written description requirement for all of the reasons detailed with respect to claim 1. In addition, claim 8, as amended, is directed toward cyclooxygenase-2 selective inhibitors and selective leukotriene B_4 receptor antagonist having a defined structure as well as a defined function.

B. ***The combination of claims 1-4 and 6-9 is enabled by the specification***

Reconsideration is requested of the rejection of claims 1-4 and 6-9. These claims were rejected on the asserted basis that they are not sufficiently enabled.

Claim 1, as amended, is directed toward a combination comprising a cyclooxygenase-2 selective inhibitor and a selective leukotriene B_4 receptor antagonist.

To satisfy the enablement requirement, a skilled artisan must be able to make or use the **claimed** invention from the disclosures in the application coupled with

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[12]See pages 5-6 and 11-18 of the specification.

[13]See pages 8-9 of the specification.

information known in the art without undue experimentation .[14] In this case, the specification details a functional definition for both the cyclooxygenase-2 selective inhibitor and the selective leukotriene B_4 receptor antagonist.[15] The specification also discloses over 100 examples of compounds that selectively inhibit cyclooxygenase-2[16] and over 40 examples of compounds that are selective leukotriene B_4 receptor antagonist.[17] In addition, protocols are provided detailing how to make a number of species of each compound.[18] Moreover, while claim 1 is not limited to any particular use, the specification discloses that the combination has utility for the treatment of inflammation or inflammation associated diseases, and then goes on to list well over 50 specific different types of inflammation or associated diseases.[19] Additionally, a working example is provided detailing use of the combination of claim 1 for the treatment of arthritis.[20] In view of this disclosure, a skilled artisan could make or use the combination of claim 1 without undue experimentation.

The Office asserts that the specification is enabling for a combination of a cyclooxygenase-2 inhibitor and a leukotriene B_4 receptor antagonist that are "therapeutically-effective" against arthritis, but is not reasonably enabling for "any

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[14]U.S. v. Teletronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988).

[15]See endnote 3.

[16]See pages 5-6 and 11-18 of the specification.

[17]See pages 8-9 of the specification.

[18]See pages 27-41 of the specification detailing general synthetic schemes. In addition, see pages 2-3 of the specification incorporating several U.S. Patents that provide additional synthetic schemes detailing how to make the compounds detailed in claim 1.

[19]See pages 6-7 of the specification.

[20]See pages 41-46 of the specification.

disease state."[21] Applicants respectfully submit that the Office is not applying the correct legal standard with respect to the enablement requirement. MPEP §2164.01(c) specifically dictates:

> When a compound or composition claim is not limited by a recited use, any enabled use that would reasonable correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenamblement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

In this instance, claim 1 is not limited to the treatment of arthritis or any other specific disease states. Instead, it is directed toward a combination with no recited use. The Office acknowledges that the specification is enabling for a combination of a cyclooxygenase-2 inhibitor and a leukotriene B_4 receptor antagonist for the treatment of arthritis.[22] Consistent with MPEP §2164.01(c), therefore, claim 1 is sufficiently enabled because it is not limited to any recited use and the specification is enabling with respect to use of the combination for the treatment of arthritis. In addition, claims 2-4 and 6-9 depend from claim 1, and satisfy the enablement requirement for all of the reasons detailed with respect to claim 1.

III. 35 U.S.C.112, Second Paragraph Rejections

Reconsideration is requested of the rejection of claims 2-4 and 6-9 under 35 U.S.C. §112, second paragraph. In support of this rejection, the Office has asserted that claims 2-4 and 6-9 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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[21]See Paper 9 at page 6.

[22]See Paper 9 at page 6.

The Office has rejected claims 2 and 9 as being indefinite regarding the attachment of R^1 to A. In accordance with the Office's suggestion, claims 2 and 9 have been amended to recite "R^1 is **a** substituent selected from..." instead of "R^1 is **at least one** substituent selected from...". The basis for this rejection, therefore, has been removed.

Claims 2, 6, 7, and 9 have also been rejected for being in improper Markush format. In accordance with the Office's suggestion, the term "or" has been replaced by "and" in the recitation of possible substituents for R^3. The basis for this rejection, therefore, has been removed.

Claim 8 has been rejected as being indefinite due to the phrase "The combination of claim 7 selected from compounds...." In response, this phrase has been replaced with "The combination of claim 3 wherein the cyclooxygenase-2 selective inhibitor is selected from...." The basis for this rejection, accordingly, has been removed.

IV. 35 U.S.C. §102 Rejection

Reconsideration is requested of the rejection of claim 1 under § 102(b) or (e) as anticipated by Buchmann et al.[23]

Buchmann et al. generally disclose a class of compounds that are leukotriene B_4 receptor antagonists. The cited art also discloses that their leukotriene B_4 receptor antagonists may be combined with one of several classes of compounds, one of which is a cyclooxygenase inhibitor.

In contrast, claim 1, as amended, is directed toward a combination comprising a cyclooxygenase-2 **selective** inhibitor and a selective leukotriene B_4 receptor antagonist. Within the context of the present invention, cyclooxygenase-2 selective inhibitors are defined as follows:

> ...compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2

[23]U.S. Patent No. 5,559,134.

> IC_{50} of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID induced side effects.[24]

Nowhere does Buchmann et al. disclose the combination of a leukotriene B_4 receptor antagonist with a cyclooxygenase-2 **selective** inhibitor as required by the combination of claim 1. Buchmann et al.'s cyclooxygenase inhibitor is **not** a cyclooxygenase-2 selective inhibitor. A claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference.[25] Because Buchmann et al. do not disclose every element of claim 1, the reference does not anticipate claim 1.

V. 35 U.S.C. §103 Rejection

Reconsideration is requested of the rejection of claims 1-4 and 6-9 under § 103(a) as obvious over Ducharme et al.[26] and Rainsford[27].

Claim 1, as amended, is directed toward a combination comprising a cyclooxygenase-2 selective inhibitor and a selective leukotriene B_4 receptor antagonist.

In contrast, Ducharme et al. disclose a class of phenyl heterocycles that selectively inhibit cyclooxygenase-2.[28] Although Ducharme et al. disclose that these compounds may be used in co-therapies with acetominophen or phenacetin; a

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[24]See pages 7-8 of the Specification.

[25]Verdegaal Bros. v. Union Oil Co. of Calif., 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP §2131.

[26]Ducharme et al., U.S. Patent No. 5,474,995.

[27]Rainsford, K.D. (1993) Agents and Actions 39:C24-C26.

[28]See Ducharme et al., at col. 2, lines 5-20.

potentiator such as caffeine; an H_2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; a sedating or non-sedating antihistamine,[29] they **do not** disclose combining a cyclooxygenase-2 selective inhibitor and a selective leukotriene B_4 receptor antagonist, as required by claim 1.

Rainsford discloses an increase in leukotriene C_4 production in the gastric circulation of both pigs and mice shortly after the administration of indomethacin. He/she also discloses that administering MK-866 both prior to and after the administration of indomethacin resulted in a decrease in the formation of gastrointestinal lesions in both animals. Nowhere does Rainsford disclose combining a cyclooxygenase-2 selective inhibitor and a selective leukotriene B_4 receptor antagonist, as required by claim 1.

The Office asserts it would have been obvious to substitute the cyclooxygenase-2 selective inhibitors disclosed in Ducharme et al. for indomethacin (a NSAID) in the preparation containing both indomethacin and MK-886 (a leukotriene B_4 receptor antagonist) disclosed in Rainsford because Ducharme et al. discloses that their cyclooxygenase-2 selective inhibitors "will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein they are presently co-administered with other agents."[30] But for the reasons stated below, the combined teachings of the references are actually away from the Offices' proposed substitution.

Rainsford discloses the co-administration of a NSAID (i.e. indomethacin) with a leukotriene B_4 receptor antagonist (MK-886). But Rainsford discloses that the purpose of administering the leukotriene B_4 receptor antagonist with the NSAID **is to reduce**

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[29]Id., at col. 8, lines 5-15.

[30]See Paper 9 at page 15.

gastrointestinal damage from non-selective cyclooxygenase inhibition by NSAIDs.[31] Ducharme et al. disclose that a benefit of cyclooxygenase-2 **selective** inhibitors, when compared to NSAIDs such as the one employed in the composition disclosed in Rainsford, is that cyclooxygenase-2 selective inhibitors have "diminished ability to induce" side-effects associated with NSAIDs, such **as gastrointestinal side effects.**[32] As such, one following Ducharme's instruction to use cyclooxygenase-2 selective inhibitors would have no need to follow Rainsford's suggestion to add a leukotriene B_4 receptor antagonist to prevent gastrointestinal damage, and thus would not be motivated by these references to do so. There is no motivation, either express or implied, to make the proposed combination. Accordingly, a skilled artisan empowered with the cited art cannot fairly be deemed to be motivated to substitute the cyclooxygenase-2 selective inhibitors disclosed in Ducharme et al. for the NSAID in the composition containing a NSAID and a leukotriene B_4 receptor antagonist as disclosed in Rainsford. As stated in MPEP 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious.

It is also significant that Ducharme et al., as noted by the Office, do disclose that their cyclooxygenase-2 selective inhibitors may be an "alternative" or a "partial or complete substitute" for "conventional NSAID's in preparations wherein they are presently co-administered with other agents or ingredients."[33] Ducharme et al. disclose a rather exhaustive list of as many as 20 different classes of compounds[34] that may be administered with their cyclooxygense-2 selective inhibitor and conspicuously **fail** to suggest administering cyclooxygenase-2 selective inhibitors with leukotriene B_4 receptor antagonists. The examples and preferences disclosed in a prior art reference must be considered, and can provide sufficient teaching away to defeat an inference of

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[31]See Rainsford, abstract.

[32]See Ducharme et al., at col. 1, lines 15-65.

[33]Id., at col. 7, lines 65-68.

[34]See Ducharme et al., at col. 8, lines 5-15.

obviousness. See, e.g., Ex parte Thumm, 132 USPQ 66, 68 (PTO Bd of Apps 1960). At the very least, Ducharme et al.'s presentation of this list and their failure to combine the two components is an absence of motivation requiring the Office to find motivation for the combination outside the reference, which has not been done.

In view of the lack of motivation to make the stated combination, it is respectfully submitted that the proposed combination amounts to an impermissible hindsight reconstruction of the elements of applicants' claims using applicants' claims as a guide.

Considering the cited art collectively, therefore, a skilled artisan would not be motivated thereby to combine a cyclooxygenase-2 selective inhibitor with a leukotriene B_4 receptor antagonist. The Office has therefore not established a *prima facie* case that the subject matter of claim 1 would have been obvious to a person of ordinary skill in the art at the time of applicants' invention in view of Ducharme et al. and Rainsford. Moreover, claims 2-4 and 6-9, which depend from claim 1, are patentable over the cited art for all of the reasons identified for claim 1.

VI. Non-statutory Double Patenting Rejection

Claims 1-4 and 6-9 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,136,839. Applicants file herewith a terminal disclaimer disclaiming the amount of any patent term on a patent issuing from this application which extends beyond the patent term of U.S. Patent No. 6,136,839 in order to obviate this rejection. Applicants, accordingly, respectfully request reconsideration and withdrawal of the non-statutory double patenting rejection.

VII. Election of Species

The PTO did not examine claims 5 [and 6] pursuant to an election of species requirement. Claims 5 and 6, though not specifically examined, depend from generic claims 2 and 4 submitted to be patentable for the reasons stated herein. As such, notwithstanding the election of species requirement, if a Notice of Allowance is issued,

claims 5 and 6 not examined are to be included among the allowable claims and in the eventually issued patent.

VIII. Conclusion

In light of the foregoing, the Applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of claims 1-9. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

If there are any additional charges in this matter, please charge our Deposit Account No. 19-1345

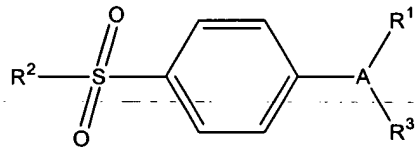
VERSION WITH MARKINGS TO SHOW CHANGES MADE

Substitute claim 1 with the following:

1. (once amended) A combination comprising [a therapeutically-effective amount of] a cyclooxygenase-2 **selective** inhibitor and a **selective** leukotriene B_4 receptor antagonist.

Substitute claim 2 with the following:

2. (three times amended) A combination comprising [a therapeutically-effective amount of] a **selective** leukotriene B_4 receptor antagonist and a cyclooxygenase-2 **selective** inhibitor selected from Taisho NS-398 (Methanesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]), meloxicam (2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide), flosulide (Methanesulfonamide, –[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]), Merck MK-966 (2(5H)-Furanone, 4-[4-(methylsulfonyl)phenyl]-3-phenyl), Merck L-752,860 and compounds of Formula I



wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R^1 [is at least one] **is independently selected from the group consisting of** [substituent selected from] heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsufinyl, halo, alkoxy and alkylthio;

wherein R^2 is methyl or amino; and

wherein R^3 is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

[or] **and** a pharmaceutically-acceptable salt thereof.

Substitute claim 3 with the following:

3. (twice amended) The combination of Claim 2 wherein the **selective** leukotriene B_4 receptor antagonist is selected from Bayer Bay-x-1005 ((R)-a-Cyclopentyl-4-(2-quinolinylmethoxy) benzene acetic acid), Ciba-Geigy CGS-25019C (Benzamide, 4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)-, (2Z)-2-butenedioate), ebselen (1,2-Benzisoselenazol-3(2H)-one, 2-phenyl), Leo Denmark ETH-615 (Benzoic acid, 4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl]), Lilly LY-293111 (Benzoic acid, 2-[3-[3-[(5-ethyl-4'-fluoro-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-2-propylphenoxy]), Ono ONO-4057 (Benzenepropanoic acid, 2-(4-carboxybutoxy)-6-[[(5E)-6-(4-methoxyphenyl)-5-hexenyl]oxy]), Terumo TMK-688 (Carbonic acid, 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester), Boehringer Ingleheim BI-RM-270 (2-Benzoxazolamine, N-[(1S)-2-cyclohexyl-1-(2-pyridinyl)ethyl]-5-methyl), Lilly LY 213024 (Benzenepropanoic acid, 5-(3-

carboxybenzoyl)-2-(decyloxy)), Lilly LY 264086 (9H-Xanthene-4-propanoic acid, 7-carboxy-3-(decyloxy)-9-oxo), Lilly LY 292728, Ono ONO-LB457 (Benzenepropanoic acid, 2-(4-carboxybutoxy)-6-[[(5E)-6-(4-methoxyphenyl)-5-hexenyl]oxy]), Pfizer 105696, Perdue Frederick PF 10042 (Pyrrolidine, 1-[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl]), Rhone-Poulenc Rorer RP 66153 (2-Thiopheneheptanoic acid, .alpha.,.alpha.-dimethyl-3-(3-phenylpropyl)), SmithKline Beecham SB-201146 (2-Propenoic acid, 3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-, (2E)), SmithKline Beecham SB-201993 (Benzoic acid, 3-[[[[6-[(1E)-2-carboxyethenyl]-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl]), Searle SC-53228 (2H-1-Benzopyran-2-propanoic acid, 7-[3-[2-(cyclopropylmethyl)-3-methoxy-4- [(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-, (2S)), Sumitamo SM 15178 (.beta.-Alanine, N-[[6-[(4-acetyl-2-ethyl-5-hydroxyphenoxy)methyl]-2- pyridinyl]carbonyl]-N-ethyl), American Home Products WAY 121006 ([1,1'-Biphenyl]-4-acetic acid, 2-fluoro-4'-(2-quinolinylmethoxy)), Bayer Bay-o-8276, calcitriol (9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)), Warner-Lambert CI-987 (2,4-Thiazolidinedione,5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]), Merck and Co. L-651392 (3H-Phenothiazin-3-one, 4-bromo-2,7-dimethoxy), Lilly LY 210073, Lilly LY 223982 (Benzenepropanoic acid, 5-(3-carboxybenzoyl)-2-[[(5E)-6-(4-methoxyphenyl)-5-hexenyl]oxy]), Lilly LY-233569 (2-Propenamide, N-hydroxy-N-methyl-3-[2-(methylthio)phenyl]), Lilly LY-255283 (Ethanone, 1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl]), Merck and Co. MK-591 (1H-Indole-2-propanoic acid, 1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-a,a-dimethyl-5-(2-quinolinylmethoxy)-, sodium salt), Merck and CO. MK-886 (1H-indole-2-propanoic acid, 1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-a,a-dimethyl-5-(1-methylethyl)), Ono ONO-LB-448, Purdue Frederick PF-5901 (Benzenemethanol, a-pentyl-3-(2-quinolinylmethoxy)), Rhone-Poulenc Rorer RG 14893 (2-Naphthalenecarboxylic acid, 4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)), Rhone-Poulenc Rorer RP 66364, Rhone-Poulenc Rorer RP 69698 (Pyridine, 2-[[5-methyl-5-(1H-tetrazol-5-

yl)hexyl]oxy]-4,6-diphenyl), Searle SC-41930 (2H-1-Benzopyran-2-carboxylic acid, 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl), Searle SC-50505, Searle SC-51146, SmithKline Beecham SK&F-104493 (5H-Pyrrolo[1,2-a]imidazole, 6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)), and Teinjin TEI-1338 (Benzoic acid, 2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino]-, methyl ester, [1R-[1.alpha.,2.beta.(E)]]).

Substitute claim 4 with the following:

4. (twice amended) The combination of Claim 3 wherein the **selective** leukotriene B_4 receptor antagonist is selected from Bayer Bay-x-1005 ((R)-a-Cyclopentyl-4-(2-quinolinylmethoxy)benzeneacetic acid), Ciba-Geigy CGS-25019C (Benzamide, 4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)-, (2Z)-2-butenedioate), ebselen (1,2-Benzisoselenazol-3(2H)-one, 2-phenyl), Leo Denmark ETH-615 (Benzoic acid, 4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl]), Lilly LY-293111 (Benzoic acid, 2-[3-[3-[(5-ethyl-4'-fluoro-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-2-propylphenoxy]), Ono ONO-4057 (Benzenepropanoic acid, 2-(4-carboxybutoxy)-6-[[(5E)-6-(4-methoxyphenyl)-5-hexenyl]oxy]), Terumo TMK-688 (Carbonic acid, 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester), Boehringer Ingleheim BI-RM-270 (2-Benzoxazolamine, N-[(1S)-2-cyclohexyl-1-(2-pyridinyl)ethyl]-5-methyl), Lilly LY 213024 (Benzenepropanoic acid, 5-(3-carboxybenzoyl)-2-(decyloxy)), Lilly LY 264086 (9H-Xanthene-4-propanoic acid, 7-carboxy-3-(decyloxy)-9-oxo), Lilly LY 292728, Ono ONO LB457 (Benzenepropanoic acid, 2-(4-carboxybutoxy)-6-[[(5E)-6-(4-methoxyphenyl)-5-hexenyl]oxy]), Pfizer 105696, Perdue Frederick PF 10042 (Pyrrolidine, 1-[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl]), Rhone-Poulenc Rorer RP 66153 (2-Thiopheneheptanoic acid, .alpha.,.alpha.-dimethyl-3-(3-phenylpropyl)), SmithKline Beecham SB-201146 (2-Propenoic acid, 3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-, (2E)), SmithKline Beecham SB-201993 (Benzoic

acid, 3-[[[[6-[(1E)-2-carboxyethenyl]-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl]), Searle SC-53228 (2H-1-Benzopyran-2-propanoic acid, 7-[3-[2-(cyclopropylmethyl)-3-methoxy-4- [(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-, (2S)), Sumitamo SM 15178 (.beta.-Alanine, N-[[6-[(4-acetyl-2-ethyl-5-hydroxyphenoxy)methyl]-2- pyridinyl]carbonyl]-N-ethyl), and American Home Products WAY 121006 ([1,1'-Biphenyl]-4-acetic acid, 2-fluoro-4'-(2-quinolinylmethoxy)).

Substitute claim 5 with the following:

5. (twice amended) The combination of Claim 4 wherein the **selective** leukotriene B_4 receptor antagonist is selected from Bayer Bay-x-1005 ((R)-a-Cyclopentyl-4-(2-quinolinylmethoxy)benzeneacetic acid), Ciba-Geigy CGS-25019C (Benzamide, 4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)-, (2Z)-2-butenedioate), ebselen (1,2-Benzisoselenazol-3(2H)-one, 2-phenyl), Leo Denmark ETH-615 (Benzoic acid, 4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl]), Lilly LY-293111 (Benzoic acid, 2-[3-[3-[(5-ethyl-4'-fluoro-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-2-propylphenoxy]), Ono ONO-4057 (Benzenepropanoic acid, 2-(4-carboxybutoxy)-6-[[(5E)-6-(4-methoxyphenyl)-5-hexenyl]oxy]), and Terumo TMK-688 (Carbonic acid, 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester).

Substitute claim 6 with the following:

6. (once amended) The combination of Claim 2 wherein A is selected from 5- or 6-member partially unsaturated heterocyclyl, 5- or 6-member unsaturated heterocyclyl, 9- or 10-member unsaturated condensed heterocyclyl, lower cycloalkenyl and phenyl; wherein R1 is selected from 5- or 6-membered heterocyclyl, lower cycloalkyl, lower cycloalkyenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R1 is optionally substituted at a substitutable position with one or more radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lowerhydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, lower

alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R2 is methyl or amino; and wherein R3 is a radical selected from hydrido, oxo, cyano, carboxyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, halo, lower alkyl, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclyl, lower hydroxyalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl, lower alkylamino, lower aminoalkyl, lower alkylaminoalkyl, phenyloxy, [and] lower aralkoxy; **[**or**]** **and** a pharmaceutically-acceptable salt thereof.

Substitute claim 7 with the following:

7. (once amended) The combination of Claim 6 wherein A is selected from oxazolyl, isoxazolyl, thienyl, dihydrofuryl, furyl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl, and pyridyl; wherein R1 is selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals, and phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, carboxyl, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl, trifluoromethoxy, hydroxyl, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, and methylthio; wherein R2 is methyl or amino; and wherein R3 is a radical selected from hydrido, oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxylmethyl, hydroxylpropyl, benzyl, formyl, phenylcarbonyl, ethoxymethyl,

furymethyloxy, aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, benzyloxy, [and] phenyloxy; [or] **and** a pharmaceutically-acceptable salt thereof.

Substitute claim 8 with the following:

8. (once amended) The combination of Claim 3 **wherein the cyclooxygenase-2 selective inhibitor is** selected from [compounds and their pharmaceutically-acceptable salts, of] the group consisting of

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; [and]
4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide[.];
3-[(3-Chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one;
8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a);
5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone ;
5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;
4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;
4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene ;
4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;
4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;
5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;
6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;
4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-

yl]benzenesulfonamide;

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;
N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;
4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;
2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;
5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;

4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;

6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone;

6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;

4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;

[2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid;

N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide;

N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide;

N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, soldium salt;

N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide;

3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one;

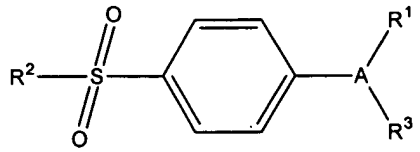
(5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4(5H)-thiazolone;

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide;
(6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid;
4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one;
6-dioxo-9H-purin-8-yl-cinnamic acid;
4-[4-(methyl)-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;
4-(5-methyl-3-phenyl-4-isoxazolyl);
2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine;
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl];
N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl];
4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridzainone;
2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid; and
[2-(2,4-dichloro-6-ethyl-3,5-dimethyl-phenylamino)-5-propyl-phenyl]-acetic acid .

Substitute claim 9 with the following:

9. (three times amended) A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a **selective** [therapeutically-effective amount of a] leukotriene B_4 receptor antagonist and a cyclooxygenase-2 **selective** inhibitor selected from Taisho NS-398 (Methanesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]), meloxicam (2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide), flosulide (Methanesulfonamide, N-[6-(2,4-

difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]), Merck MK-966 (2(5H)-Furanone, 4-[4-(methylsulfonyl)phenyl]-3-phenyl), Merck L-752,860 and compounds of Formula I



wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R^1 [is at least one] **is independently selected from the group consisting of** [substituent selected from] heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsufinyl, halo, alkoxy and alkylthio;

wherein R^2 is methyl or amino; and

wherein R^3 is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

[or] **and** a pharmaceutically-acceptable salt thereof.

If there are any additional charges in this matter, please charge Deposit Account No. 19-1345

Respectfully submitted

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